REMARKS

Applicants note that the present Office Action was sent to Applicants' previous counsel. As indicated in the Revocation and New Power of Attorney and Change of Address documents (mailed March 7, 2003), Applicants' new counsel and address are indicated herein. Applicants request that all correspondence from the U.S. Patent & Trademark Office be sent to the current address in order to avoid delays. If there are any questions, please don't hesitate to contact the undersigned.

The present case was originally filed with 28 Claims. In a Restriction Requirement mailed December 17, 2002, the Examiner restricted the Claims into four Groups, with Claims 1-8 and 11-16 in Group I; Claims 1-7, 9, and 11-16 in Group II; Claims 1-7 and 11-16 in Group III; and Claims 17-28 in Group IV. In a Response mailed January 15, 2003, Applicants elected the Claims in Group IV (Claims 17-28) with traverse. In the present Response, Claims 1-16 are cancelled without prejudice. Applicants reserve the right to pursue these Claims in subsequently filed Divisional and/or Continuation application(s). Thus, Claims 17-28 were pending in the present application. Applicants have added new Claims 29-39, to claim additional embodiments of the recipient mouse of the present invention. Applicants believe that these Claims find support throughout the Specification and the art and that no new matter is added. Thus, upon entry of the present amendments, Claims 17-39 are pending in this application.

The Examiner has objected to Claim 28 for the typographical error in the term "Drab." Applicants have corrected this typographical error. Thus, the Claim correctly recites "DRab." The Examiner's rejections are addressed in the following order below:

1) Claims 17-28 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement.

2) Claims 17-28 stand rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled; and

3) Claims 22-28 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

1) Claims 17-28 Meet the Written Description Requirement

The Examiner has rejected Claims 17-28 under 35 U.S.C. §112, first paragraph as allegedly not meeting the written description requirement. In particular, the Examiner argues that the present Specification "fails to teach a representative number of species of claimed transgenic recipient mice having a disruption of both alleles of any gene involved in lymphocyte maturation and having any phenotype as encompassed by the scope of the instant claims, and any methods for making the same transgenic recipient mice. The state of the art at the filing date of the present application does not provide such guidance, particularly the state of transgenesis is known to be highly unpredictable with respect to the attainment of any desired phenotype. . . . The skilled artisan cannot envision the detailed structure of a transgenic recipient mouse as broadly claimed and broadly claimed methods for making the same, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method." (Office Action, page 4). Applicants note that the Examiner admits that the present Specification provides a written description of making 4D1/C2D/RAG-2 mice that express surface DR and not I-Eα, and wherein the mice appear to have functional immune responses. (Office Action, page 4).

Applicants must respectfully disagree with the Examiner's arguments and the characterization of the present Specification and the art at the time the present application was filed. Nonetheless, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended Claim 17 to recite that the disruption in both alleles of a gene involves a gene which modulates VDJ recombination such that lymphocyte maturation does not occur. Support for this amendment is found in the Specification as filed (*See e.g.*, page 3, lines 5-6). No new matter is added by this amendment. Applicants submit that this amendment overcomes the Examiner's rejection based on the argument that the present Specification does not provide a written description for a disruption in both alleles of any gene involved in lymphocyte maturation, as the present application clearly provides support for the disruption in alleles associated with VDJ recombination.

In addition, the Claims now recite that the animals are immunodeficient. Support for this amendment is clearly provided in the Specification as filed (*See e.g.*,

page 10, lines 22-30). Thus, the Examiner's argument that the animals have any phenotype is rendered moot.

Applicants' Claims further recite that the human MHC Class II transgene is incorporated into the genome of the recipient mouse. This amendment is also clearly supported by the Specification as filed (*See e.g.*, page 10, line 32 through page 15, line 6).

New Claims 29-39 provide additional specific embodiments of the transgenic mice of the present invention. Applicants submit that support is provided in the Specification as filed for these new Claims.

Applicants respectfully submit that the Claims are allowable and request that the Examiner withdraw this rejection.

2) Claims 17-28 are Enabled

The Examiner further has rejected Claims 17-28 under 35 U.S.C. §112, first paragraph as allegedly not being enabled. In particular, the Examiner argues that the present Specification "does not reasonably provide enablement for a recipient mouse comprising a disruption in both alleles of any gene involved in lymphocyte maturation, and containing a human transgene comprising a nucleic acid sequence that encodes a MHC Class II DR molecule, wherein the transgene comprises naturally linked DRab and DQab alleles with any phenotype; and any method for making the same recipient mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." (Office Action, pages 5-6; emphasis original).

Applicants note that the Examiner admits that the present Specification is "enabling for a recipient mouse whose genome comprises a disruption in both alleles of the RAG-2 gene, and a human transgene comprising a nucleic acid sequence that encodes a MHC Class II DR molecule, wherein the transgene comprises naturally linked DRab and DQab alleles; and a method of making the same recipient mouse, said method comprises the introduction of said human transgene into a transgenic mouse whose genome comprises a disruption in both alleles of the RAG-2 gene in a background deficient for murine I-Eα through breeding." (Office Action, page 5).

The Examiner argues that the breadth of the Claims is not enabled, due to the state and unpredictability of the art at the time the application was filed and the amount of guidance provided in the Specification. Applicants must respectfully disagree. In terms of the breadth of the Claims, as indicated above, Applicants have amended the Claims without prejudice to more clearly set forth the characteristics of the claimed animals and methods. Thus, Applicants respectfully submit that the breadth of the Claims is enabled by the Specification as filed.

In terms of the unpredictability of the art, Applicants respectfully submit that at the time the Specification was filed, the expression of human HLA Class II transgenes in transgenic animals derived from the use of large fragments of human genomic DNA provides a sufficient amount of regulatory information for the long-term and functional expression of MHC Class II molecules in transgenic mice. For example, at the time the present application was filed, transgenic animals comprising HLA DR2 (*See*, Gonzalez-Gay *et al.*, Hum. Immunol., 50: 54-60 [1996])[2], DR3 (*See*, Straub *et al.*, Immunogenetic 40:104-108 [1994]), DQ6 (*See*, Nishimura *et al.*, J. Immunol., 145:353-360 [1990]), and DQ8 (*See*, Wen *et al.*, J. Clin. Invest., 102:947-957 [1998]) were known and found to be capable of expressing HLA Class II molecules and mediate immune responses to various antigens. In addition, the RAG-1 gene was known (*See*, Mombaerts *et al.*, Cell 68:869-877 [1992]), as was the RAG-2 gene (Shinkai *et al.*, Cell 68:855-867 [1992]), the T-cell receptor gene (*See*. Mombaerts *et al.*, Nature 360:225-231 [1992]), and immunoglobulin genes (*See e.g.*, Chen *et al.*, Internatl. Immunol., 5:647-656 [1993]). In addition, I-Eα and I-Aβ and their effects were well known (*See*, Mathis et al., Proc. Natl. Acad. Sci. 80:273-277 [1983]; and Cosgrove et al., Cell 66:1051-1066 [1991]). Thus, contrary to the Examiner's arguments, there was sufficient predictability in the art at the time the application was filed to support the claimed invention. In addition, the present Specification as filed provides in-depth descriptions of how transgenic animals can be produced, screened for various phenotypic characteristics, and utilized.

3) The Claims are Definite

The Examiner has rejected Claims 22-28, as allegedly being indefinite. In particular, the Examiner argues that the Claims are incomplete for omitting essential

[2] Each of the references cited herein will be provided in the near future.

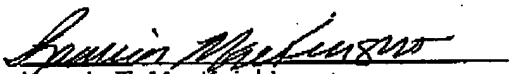
components and/or essential steps The Examiner argues that "it is unclear how both alleles of a gene involved in lymphocyte maturation (*e.g.*, RAG-2 gene) are disrupted and in which cells the disruption is carried out; and how a transgene comprising a nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked is inserted and in which which cells; and how murine I-Eα is inactivated to make the recipient mouse as claimed." (Office Action, at page 12).

Applicant must respectfully disagree with the Examiner's arguments. The present Specification as filed provides a detailed description of methods suitable to disrupt genes involved in lymphocyte maturation, as well as how transgenes are inserted, the cell types, and inactivation of I-Eα and I-Ab (*See e.g.*, the Detailed Description of the Invention). However, it is not intended that the present Claims be limited to any specific means for gene disruption, introduction of transgenes, and/or inactivation of I-Eα is accomplished, as those of skill in the art will appreciate that various methods find use with the present invention. Applicants respectfully submit that based on the present Specification and the knowledge of those of skill in the art, the present Claims are definite. Thus, Applicants respectfully request that this rejection be withdrawn and the Claims passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Office Action of March 27, 2003, having been addressed, reconsideration of the Claims is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned at (650) 846-5838.

Dated: 26 September 2003



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